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ORIGINAL ARTICLE

Oral adverse effects of drugs: Taste disorders

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Abstract

Objective: Oral healthcare professionals are frequently confronted with patients using drugs on a daily basis. These drugs can cause taste disorders as adverse effect. The literature that discusses drug-induced taste disorders is fragmented. This article aims to support oral healthcare professionals in their decision making whether a taste disorder can be due to use of drugs by providing a comprehensive overview of drugs with taste disorders as an adverse effect.

Materials and methods: The national drug information database for Dutch pharmacists, based on scientific drug information, guidelines, and summaries of product characteristics, was analyzed for drug-induced taste disorders. "MedDRA classification" and "Anatomic Therapeutic Chemical codes" were used to categorize the results.

Results: Of the 1,645 drugs registered in the database, 282 (17%) were documented with "dysgeusia" and 61 (3.7%) with "hypogeusia." Drug-induced taste disorders are reported in all drug categories, but predominantly in "antineoplastic and immunomodulating agents," "antiinfectives for systemic use," and "nervous system." In ~45%, "dry mouth" coincided as adverse effect with taste disorders.

Conclusion: Healthcare professionals are frequently confronted with drugs reported to cause taste disorders. This article provides an overview of these drugs to support clinicians in their awareness, diagnosis, and treatment of drug-induced taste disorders.

KEYWORDS

drug-induced taste disorders, drugs adverse effects, dysgeusia, hypogeusia, oral adverse effects

1 | INTRODUCTION

The global consumption of drugs to treat acute and chronic diseases continues to increase (WHO, 2011). Inevitably, healthcare professionals are frequently confronted with patients using one or more drugs on a daily basis. These drugs can cause adverse effects in the oral region such as xerostomia, hyposalivation, mucositis, and taste disorders.

Due to the large number of different drugs available and their wide range of adverse effects, it is difficult and time-consuming for healthcare professionals to take all the potential consequences into account during their daily practice. To support oral healthcare professionals in their decision making, the journal of Oral Diseases will publish a series of articles discussing the most frequent adverse effects of drugs in the oral region. The

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ATC level

1: **A** Alimentary tract and metabolism
 2: **A07** Antidiarrheal, intestinal anti-inflammatory/infective agents
 3: **A07A** Intestinal antiinfectives
 4: **A07AC** Imidazole derivatives
 5: **A07AC01** Miconazole oral gel

1: **G** Genitourinary system and sex hormones
 2: **G01** Gynecological antiinfectives and antiseptics
 3: **G01A** Antiinfectives and antiseptics, excl. combinations with corticosteroids
 4: **G01AF** Imidazole derivatives
 5: **G01AF04** Miconazole vaginal gel

1: **D** Dermatologicals
 2: **D01** Antifungals for dermatological use
 3: **D01A** Antifungals for topical use
 4: **D01AC** Imidazole and triazole derivatives
 5: **D01AC02** Miconazole (cutaneous)

1: **S** Sensory organs
 2: **S02** Otologicals
 3: **S02A** Antiinfectives
 4: **S02AA** Antiinfectives
 5: **S02AA13** Miconazole ear drops

FIGURE 1 Hierarchy of ATC levels for miconazole [Colour figure can be viewed at wileyonlinelibrary.com]

first paper in this series discusses drug-induced taste disorders (DITD).

Fark, Hummel, Hahner, Nin, and Hummel (2013) divided taste disorders into quantitative taste disorders and qualitative taste disorders. Quantitative taste disorders include hypergeusia (an abnormally heightened sense of taste), normogeusia (a normal sense of taste), hypogeusia (an abnormally lowered sense of taste), and ageusia (a lacking sense of taste). Qualitative taste disorders are dysgeusia (a distortion in sense taste) and phantogeusia (a taste perception without a stimulus) (Fark et al., 2013). Although disturbances in taste seem harmless, they can interfere with a patients' social behavior by avoiding dinners or lead to a change in diet which can, among others, cause weight loss, nutrient deficiencies, or overweight due to excessive use of salt and sugar to compensate bad flavors (Noel, Sugrue, & Dando, 2017). As such, taste disorders can lead to a significant reduction in the quality of life (Ponticelli et al., 2017). Therefore, it is important that oral healthcare professionals are aware of the possible causes and treatment modalities of taste disorders. Adverse effects of drugs account for 9%–22% of the taste disorders (Fark et al., 2013; Hamada, Endo, & Tomita, 2002). This article aims to support oral healthcare professionals in their decision making whether a taste disorder can be due to use of drugs by providing a comprehensive overview of drugs documented with taste disorders as an adverse effect.

2 | MATERIALS AND METHODS

2.1 | Data source

The Informatorium Medicamentorum (IM) of the Royal Dutch Pharmacists Association (KNMP) is the leading national drug information database and reference work for pharmacists in the Netherlands. This database is based on scientific drug information, guidelines, and summaries of product characteristics (SmPCs) (KNMP, 2019). The IM is updated every 2 weeks with the latest available information

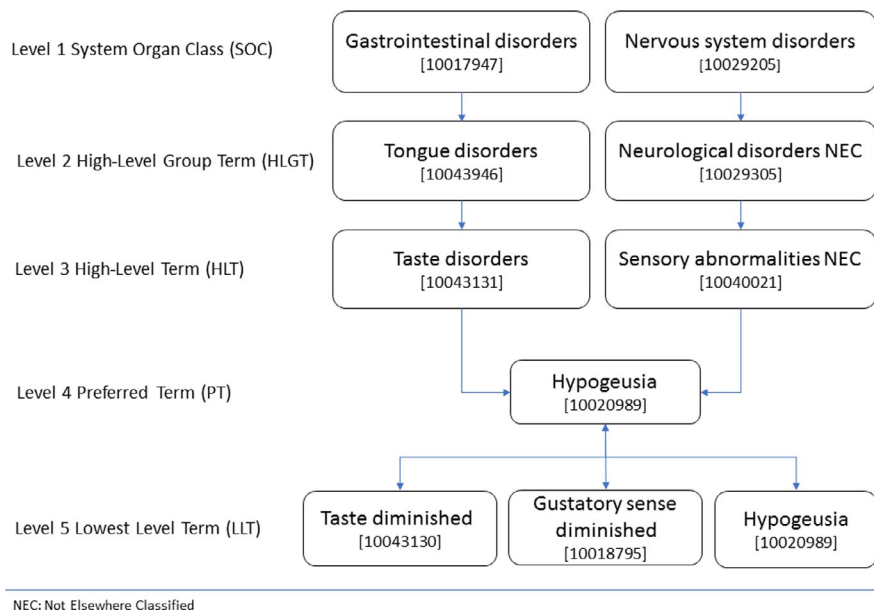
from scientific publications, warnings of authorities, and SmPCs of the European Medicines Agency and Medicines Evaluation Board in the Netherlands.

The IM was last searched on August 1, 2018, and all data regarding adverse effects available at that time were included in this study. Of each drug, the category "side effects" from the IM was searched for taste disorders and synonyms (e.g., dysgeusia).

The following characteristics of drugs causing DITD were registered: generic name of the drug, term of the adverse effect, incidence of the adverse effect, and Anatomic Therapeutic Chemical (ATC) codes of the drug. The ATC classification was developed by the World Health Organization and categorizes all active substances in drugs according to a hierarchy with five levels. It serves as a tool for exchanging data on drug use on a national and international level (WHO, 2003). It is worth noting that one active substance can be used in different drugs with different treatment goals. Therefore, it is possible that one active substance (e.g., miconazole) has several ATC codes (Figure 1).

Originally, the terms used to describe one adverse effect (e.g., taste disorders) in the SmPCs varied between drugs and throughout the years. In order to create a standardized structured database, the MedDRA classification was manually applied after the selection of drugs causing DITD. The MedDRA classification is developed by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human and endeavors to standardize all international medical terminology, including terms for adverse effects (Meddra, 2019). The MedDRA classification is a hierarchical system that distinguishes five levels in the categorization of medical terminology. The most specific level is the "Lowest Level Term (LLT)" and the next level is called the "Preferred Term (PT)." Each LLT is directly linked to only one PT. Each PT is linked to at least one LLT (itself) and sometimes several synonyms of the LLT. In Figure 2, the PT "Hypogeusia" is presented with its LLTs. After the selection of drugs related to DITD from the IM, the adverse effect terms were first matched

FIGURE 2 Hierarchy of “Hypogeusia” in MedDRA [Colour figure can be viewed at wileyonlinelibrary.com]



in accordance with the support document (Meddra, 2018), with the most applicable LLT in Dutch. Terms were then translated into English by using the LLT codes and the English version of MedDRA. The English LLT was automatically matched with the English PT level according to the MedDRA hierarchy.

Microsoft® Excel (version 16.16.1) was used to create the database with the acquired information on DITD and to perform descriptive statistics.

3 | RESULTS

In total, 1,645 drugs (active substances) were registered in the IM. Each drug can cause multiple adverse effects resulting in approximately 65,000 unique combinations between a drug and an adverse effect in the IM. Of these 65,000 combinations, 2,335 (3.5%) were defined by the authors as relevant for the oral healthcare provider and 343 (0.5%) concerned taste disorders. Of the 1,645 drugs, 314 (19%) could cause DITD. As IM discriminates different administration forms per drug, the number of drugs (314) and number of combinations (343) causing taste disorders differ. For example, “Budesonide,” which can be administered rectally, nasally, and by inhalation, is registered three times with dysgeusia as a potential adverse effect with three different incidences. Table 1 presents the different LLTs and PTs used in the IM for taste disorders and the number drugs which can potentially cause them. Taste disturbance as an adverse effect was reported in all level 1 categories of the ATC classification (Table 2).

“Normogeusia,” “hypergeusia,” “ageusia,” and “phantogeusia” were not reported in the IM.

3.1 | Dysgeusia

Dysgeusia (PT) as an adverse effect was reported 282 times (17.1% of 1,645 drugs) (Table 1). The drug categories “antineoplastic and

TABLE 1 LLTs and PT for taste disorders in IM analysis

Adverse effect term	No. of drugs
Dysgeusia (PT)	282
Dysgeusia (LLT)	15
Taste bitter (LLT)	9
Taste disturbance (LLT)	245
Taste garlic (LLT)	1
Taste metallic (LLT)	12
Hypogeusia (PT)	61
Hypogeusia (LLT)	61
Total	343

immunomodulating agents” (18.8%), “antiinfectives for systemic use” (15.6%), and “nervous system” (13.8%) account for almost half of the drug-induced dysgeusia (Table 2). Hypergeusia, ageusia, and phantogeusia were not reported.

Table 3 presents a selection of the drugs that could cause dysgeusia (PT) and comprises only the category “Alimentary tract and metabolism.” The frequencies of the adverse effect and whether a drug also causes the adverse effects “parosmia,” “anosmia,” “dry mouth,” or “hyposalivation” are presented as well, since these adverse effects are closely related to taste disorders. In some drugs, dysgeusia is only caused when the drug is administered through a specific route or under certain circumstances. The full table of all the 282 drugs causing dysgeusia is presented online as supplementary data (Table S1).

In these 282 drugs, the frequency of dysgeusia was “very common” in 7.1%, “common” in 31.2%, “uncommon” in 32.7%, and “rare or very rare” in 9.9% of the drugs. In 19.1% of the drugs, the “frequency was not known,” which means that in the IM, the frequency could not be estimated based on the available data.

Dysgeusia coincided in 114/282 drugs (40.4%) with “dry mouth” as an adverse effect, in 5/282 drugs (1.7%) with “anosmia,” in 2/282

ATC level 1 category	Dysgeusia (%)	Hypogeusia (%)	Total
Alimentary tract and metabolism	24 (8.5)	2 (3.1)	26
Antiinfectives for systemic use	44 (15.6)	7 (11.0)	51
Antineoplastic and immunomodulating agents	53 (18.8)	22 (39.0)	75
Antiparasitic products, insecticides, and repellents	5 (1.7)	-	5
Blood and blood forming organs	13 (4.6)	1 (1.4)	14
Cardiovascular system	23 (8.1)	5 (7.8)	28
Dermatologicals	13 (4.6)	2 (3.2)	15
Genitourinary system and sex hormones	5 (1.7)	3 (4.7)	8
Musculoskeletal system	12 (4.3)	2 (3.1)	14
Nervous system	39 (13.8)	12 (19.0)	51
Respiratory system	16 (5.7)	-	16
Sensory organs	10 (3.5)	1 (1.5)	10
Systemic hormonal preparations, excl.	7 (2.5)	2 (3.1)	9
Various	18 (6.3)	2 (3.1)	20
Total	282	61	343

TABLE 2 Number of drugs causing dysgeusia or hypogeusia per ATC level 1 category

drugs (0.7%) with "parosmia," in 6/282 drugs (2.1%) with "dry mouth and anosmia," and in 3/282 drugs (1.0%) with "dry mouth and parosmia." None of these drugs were reported to cause "hyposalivation."

Supplementary online Tables S2 and S3 present drugs that cause a bitter taste (LLT) or metallic taste (LLT), respectively. Disulfiram (N07BB01), a drug used to treat patients with alcohol abuses, was the only drug reported to cause a garlic taste (LLT).

3.2 | Hypogeusia

Drug-induced hypogeusia was reported in 61 drugs (3.7% of 1,645). Hypogeusia was predominantly reported in the drug categories "Antineoplastic and immunomodulating agents" (39.0%) and "Nervous system" (19%). Hypogeusia did not occur in the drug categories "Respiratory system" and "Antiparasitic products, insecticides and repellents" (Table 2). Table 4 presents all drugs in the IM that are reported to cause hypogeusia. In these 61 drugs, the frequency of hypogeusia was "very common" in 9.5%, "common" in 31.7%, "uncommon" in 25.4%, and "rare or very rare" in 15.9% of the drugs. In 17.5% of the drugs, the "frequency was not known." Hypogeusia coincided in 28/61 drugs (45.9%) with "dry mouth," in 1/61 drugs (1.6%) with "anosmia," and in 2/61 drugs (3.2%) with "dry mouth/anosmia." None of these drugs were reported to cause "hyposalivation."

4 | DISCUSSION

In total, 20% (343/1,645) of the drugs used in the Netherlands has been reported to potentially cause DITD (dysgeusia and hypogeusia).

DITD was reported in all ATC level 1 categories, suggesting that all healthcare professionals may frequently encounter the adverse effects of these drugs. Healthcare professionals that treat patients using antineoplastic drugs are most likely to be confronted with DITD. Despite the recorded percentage of our search, the exact incidence of DITD is unclear due to a lack of systematic well controlled clinical trials (Schiffman, 2018).

To the best of our knowledge, this study is the first comprehensive overview of DITD based on the analysis of a national drug information database which includes adverse effects. The available literature that discusses DITD is fragmented, since previous articles usually report on a specific type of patients with DITD (e.g., cancer) (de Coe & Haan, 2016; Okada et al., 2016; Tuccori et al., 2011), specific drug categories causing DITD (e.g., cardiovascular drugs) (Che, Li, Fang, Reis, & Wang, 2018; van der Werf, Rovithi, Langius, de van der Schueren, & Verheul, 2017) or summarize the literature instead of providing an overall analysis of what registered drugs are linked to DITD (Mortazavi, Shafiei, Sadr, & Safiaghdam, 2018; Schiffman, 2018; Wang, Glendinning, Grushka, Hummel, & Mansfield, 2017). In addition, the ATC classification is not always applied, making it difficult to compare the results of the various studies.

Our data source contains predominantly PT level terms. Although this is in accordance with the MedDRA guidelines, it is likely that specific LLT terms like "bitter taste" and "metallic taste" might therefore be underreported compared to previous studies which do not use the MedDRA. It also has to be mentioned that the terms and incidences used in the database (e.g., "dysgeusia", "hypoguesia") are based on patient-reported adverse effects during pharmacological developing studies or postmarketing studies. This subjective reporting by patients

**TABLE 3** Drug-induced dysgeusia (PT) in level 1 ATC category: alimentary tract and metabolism

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ALIMENTARY TRACT AND METABOLISM	Antiemetics and antinauseants	Aprepitant	A04AD12	Taste disturbance	Frequency not known	-	D
	Antipropulsives	Rolapitant	A04AD14	Taste disturbance	Uncommon (0.1%–1%)	-	-
Blood glucose-lowering drugs Excl. insulins	Antipropulsives	Loperamide	A07DA03	Taste disturbance	Frequency not known	-	D
		Exenatide	A10BJ01 A10BJ01	Taste disturbance	Uncommon (0.1%–1%)	-	-
	Blood glucose-lowering drugs Excl. insulins	Glimepiride	A10BB12	Taste disturbance	Frequency not known	-	-
		Liraglutide	A10BJ02	Taste disturbance	Common (1%–10%)	-	D
		Metformin	A10BA02	Taste disturbance	Common (1%–10%)	-	-
		Esomeprazole	A02BC05	Taste disturbance	Frequency not known	After intravenous administration	D
	Drugs for peptic ulcer and gastroesophageal reflux disease (GORD)	Famotidine	A02BA03	Taste disturbance	Uncommon (0.1%–1%)	-	D
		Lansoprazole	A02BC03	Taste disturbance	Frequency not known	-	D
		Rabeprazole	A02BC04	Taste disturbance	Frequency not known	-	D
		Fidaxomicin	A07AA12	Taste disturbance	Uncommon (0.1%–1%)	-	D
Intestinal antiinfectives	Intestinal antiinfectives	Miconazole	A07AC01 D01AC02 G01AF04 S02AA13	Dysgeusia	Common (1%–10%)	After oral administration	D
		Miconazole	A07AC01 D01AC02 G01AF04 S02AA13	Taste disturbance	Uncommon (0.1%–1%)	After oral administration	D
	Intestinal anti-inflam-matory agents	Budesonide	A07EA06 R01AD05 R03BA02	Taste disturbance	Uncommon (0.1%–1%)	After rectal administration	D,P
		Budesonide	A07EA06 R01AD05 R03BA02	Taste disturbance	Common (1%–10%)	After inhalation	D,P
		Budesonide	A07EA06 R01AD05 R03BA02	Taste disturbance	Frequency not known	After nasal administration	D,P
		Cromoglicic acid	A07EB01 R01AC01 R03BC01 S01GX01	Dysgeusia	Uncommon (0.1%–1%)	-	-
	Other alimentary tract and metabolism products	Sulfasalazine	A07EC01	Taste disturbance	Common (1%–10%)	-	A
		Agalsidase alfa	A16AB03	Taste disturbance	Common (1%–10%)	-	A
		Sodium phenylbutyrate	A16AX03	Taste disturbance	Common (1%–10%)	-	-
		Chlorhexidine	A01AB03 B05CA02 D08AC02 D09AA12 S01AX09	Taste disturbance	Rare or very rare (<0.1%)	-	-
Stomatological preparations	Stomatological preparations	Triamcinolone	A01AC01 D07AB09 H02AB08 R01AD11 S01BA05 S02BA	Taste disturbance	Rare or very rare (<0.1%)	After nasal administration	-
		Hydrogen peroxide	A01AB02	Dysgeusia	Frequency not known	-	-

Note: Abbreviations: A, anosmia; ATC, Anatomic Therapeutic Chemical; D, dry mouth; LLT, lowest level term; P, parosmia

TABLE 4 Drug-induced hypogeusia (PT) in all ATC level 1 categories

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
ALIMENTARY TRACT AND METABOLISM	Belladonna and derivatives, plain	Atropine	A03BA01 S01FA01	Hypogeusia	Frequency not known	-	D
	Intestinal antiinfectives	Colistin	A07AA10 J01XB01	Hypogeusia	Rare or very rare (<0.1%)	After inhalation	-
ANTIINFECTIVES FOR SYSTEMIC USE	Antimycotics for systemic use	Micafungin	J02AX05	Hypogeusia	Uncommon (0.1%–1%)	-	-
	Direct-acting antivirals	Darunavir	J05AE10	Hypogeusia	Frequency not known	-	D
	Drugs for treatment of tuberculosis	Rifabutin	J04AB04	Hypogeusia	Rare or very rare (<0.1%)	-	-
	Macrolides, lincosamides, and streptogramins	Clarithromycin	J01FA09	Hypogeusia	Rare or very rare (<0.1%)	-	D
	Other antibacterials	Methenamine	J01XX05	Hypogeusia	Rare or very rare (<0.1%)	-	-
	Quinolone antibacterials	Levofloxacin	J01MA12	Hypogeusia	Rare or very rare (<0.1%)	After oral and intravenous administration	-
		Ofloxacin	J01MA01 S01AE01 S02AA16	Hypogeusia	Rare or very rare (<0.1%)	After oral administration	D,A
		Capecitabine	L01BC06	Hypogeusia	Common (1%–10%)	-	D
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	Antimetabolites	Tegafur	L01BC03	Hypogeusia	Common (1%–10%)	-	D
	Hormone antagonists and related agents	Anastrozole	L02BG03	Hypogeusia	Common (1%–10%)	-	-
	Immunostimulants	Aldesleukin	L03AC01	Hypogeusia	Common (1%–10%)	-	-
	Other antineoplastic agents	Afatinib	L01XE13	Hypogeusia	Common (1%–10%)	-	-
		Axitinib	L01XE17	Hypogeusia	Very common (>10%)	-	-
		Bosutinib	L01XE14	Hypogeusia	Common (1%–10%)	-	-
		Cabozantinib	L01XE26	Hypogeusia	Common (1%–10%)	-	-
		Cisplatin	L01XA01	Hypogeusia	Frequency not known	-	-

(Continues)



TABLE 4 (Continued)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
BLOOD AND BLOOD FORMING ORGANS	Iron, parenteral preparations	Crizotinib	L01XE16	Hypogeusia	Very common (>10%)	-	-
		Dasatinib	L01XE06	Hypogeusia	Common (1%-10%)	-	-
		Everolimus	L01XE10 L04AA18	Hypogeusia	Common (1%-10%)	In case of oncologic treatment	D
		Necitumumab	L01XC22	Hypogeusia	Common (1%-10%)	-	-
		Nilotinib	L01XE08	Hypogeusia	Common (1%-10%)	-	-
		Palbociclib	L01XE33	Hypogeusia	Common (1%-10%)	-	-
		Panobinostat	L01XX42	Hypogeusia	Common (1%-10%)	-	D
		Sorafenib	L01XE05	Hypogeusia	Common (1%-10%)	-	D
		Temsirolimus	L01XE09	Hypogeusia	Common (1%-10%)	-	-
		Trastuzumab	L01XC03	Hypogeusia	Very common (>10%)	-	D
		Trastuzumab emtansine	L01XC14	Hypogeusia	Common (1%-10%)	-	D
		Vandetanib	L01XE12	Hypogeusia	Common (1%-10%)	-	D
		Vismodegib	L01XX43	Hypogeusia	Common (1%-10%)	-	-
		Ferric carboxymaltose	B03AC	Hypogeusia	Uncommon (0.1%-1%)	-	-
CARDIOVASCULAR SYSTEM	Ace inhibitors, plain	Captopril	C09AA01	Hypogeusia	Common (1%-10%)	-	D
		Enalapril	C09AA02	Hypogeusia	Frequency not known	-	D
		Ramipril	C09AA05	Hypogeusia	Uncommon (0.1%-1%)	-	D,A
		Esmolol	C07AB09	Hypogeusia	Uncommon (0.1%-1%)	-	D
		Atorvastatin plain	C10AA05	Hypogeusia	Uncommon (0.1%-1%)	-	-

(Continues)

TABLE 4 (Continued)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
DERMATOLOGICALS	Antifungals for topical use	Terbinafine	D01AE15 D01BA02	Hypogeusia	Uncommon (0.1%–1%)	–	–
	Other dermatological preparations	Tacrolimus	D11AH01 L04AD02 S01XA	Hypogeusia	Frequency not known	After intravenous administration	–
GENITOURINARY SYSTEM AND SEX HORMONES	Hormonal contraceptives for systemic use	Ulipristal	G03AD02 G03XB02	Hypogeusia	Frequency not known	When used as emergency anticonceptive	D
	Other urologicals, Incl. antispasmodics	Solifenacin	G04BD08	Hypogeusia	Uncommon (0.1%–1%)	–	D
		Tiopronine	G04BX16	Hypogeusia	Uncommon (0.1%–1%)	–	–
MUSCULO SKELETAL SYSTEM	Muscle relaxants, centrally acting agents	Baclofen	M03BX01	Hypogeusia	Uncommon (0.1%–1%)	–	D
	Specific antirheumatic agents	Penicillamine	M01CC01	Hypogeusia	Common (1%–10%)	–	–
NERVOUS SYSTEM	Anesthetics, local	Articaine	N01BB08	Hypogeusia	Frequency not known	–	–
		Cocaine	N01BC01 S01HA01	Hypogeusia	Frequency not known	–	A
		Mepivacaine	N01BB03	Hypogeusia	Frequency not known	–	–
	Antidepressants	Duloxetine	N06AX21	Hypogeusia	Uncommon (0.1%–1%)	–	D
		Maprotiline	N06AA21	Hypogeusia	Frequency not known	–	D
	Antiepileptics	Pregabalin	N03AX16	Hypogeusia	Uncommon (0.1%–1%)	–	D
		Rizatriptan	N02CC04	Hypogeusia	Uncommon (0.1%–1%)	–	D
	Antipsychotics	Paliperidone	N05AX13	Hypogeusia	Uncommon (0.1%–1%)	–	D
	Dopaminergic agents	Opicapone	N04BX04	Hypogeusia	Uncommon (0.1%–1%)	–	D
		Varenicline	N07BA03	Hypogeusia	Frequency not known	–	D
	Drugs used in addictive disorders						
	Opioids	Hydromorphone	N02AA03	Hypogeusia	Uncommon (0.1%–1%)	After oral administration	D

(Continues)

TABLE 4 (Continued)

ATC level 1	ATC level 3	Generic name	ATC Code	LLT MedDRA	Frequency	Specific type of administration	Coinciding adverse effects
	Psychostimulants, agents used for ADHD and nootropics	Dexamfetamine	N06BA02	Hypogeusia	Rare or very rare (<0.1%)	-	D
SENSORY ORGANS	Antiglaucoma preparations and miotics	Brinzolamide	S01EC04	Hypogeusia	Rare or very rare (<0.1%)	After systemic administration	D
SYSTEMIC HORMONAL PREPARATIONS, EXCL.	Antithyroid preparations	Carbimazole	H03BB01	Hypogeusia	Frequency not known	-	-
		Propylthiouracil	H03BA02	Hypogeusia	Rare or very rare (<0.1%)	-	-
VARIOUS	Allergens	Grass pollen	V01AA02 V01AA	Hypogeusia	Rare or very rare (<0.1%)	After subcutaneous administration	D
	Magnetic resonance imaging contrast media	Gadoteric acid	V08CA02	Hypogeusia	Uncommon (0.1%–1%)	After intravenous administration	-

Note: Abbreviations: A, anosmia; ATC, Anatomical Therapeutic Chemical; D, dry mouth; LLT, lowest level term.

might lead to a reporting bias or inaccuracy in terminology. The difference between objective and subjective adverse effects measuring is a common point of discussion when reporting on adverse effects and one without a clear solution. When considering taste disorders, there is no commonly used test available for objectifying taste disorders, which makes it impossible to report solely objective data. In order to make future studies on oral adverse effects more comparable, it is recommended that the MedDRA terminology and hierarchy and, if available, objective tests are used during data collection and describing the results. Homogenous reporting of results, on for instance incidences, will lead to clinically more applicable data.

Due to differences in local and regional laws and regulations on drug admission, registered drugs differ per country. Thus, there will be drugs that are reported in the current study that are not available in some countries and reverse. However, with regard to the European countries, most of the reported drugs will be available in all countries. By applying the ATC and MedDRA classification, the data are internationally applicable and could serve as a guidance for future reports on DITD.

The exact mechanisms underlying DITD are still unclear and may vary between individuals. Individual variations may be caused by polypharmacy (drug interactions), dosage differences, and patient-specific variables (e.g., genetics, age, and medical conditions) (Schiffman, 2018). Schiffman (2018) describes several presumed mechanisms behind DITD. Some drugs have sensory properties that cause a bitter or metallic taste. These drugs interact with the taste buds: (a) after oral application, (b) by diffusion into the saliva after absorption in the gut or intravenous administration, or (c) by accumulation in the taste buds when used chronically. The latter might explain why DITD can occur months or years after the initial usage (e.g., lithium carbonate). Other drugs distort taste and smell signals for sweet or salt, causing a bitter or sour taste perception of food and beverages. The garlic-like taste caused by disulfiram is due to exhalation of carbon disulfide. Drug-drug interactions can lead to elevated blood plasma levels beyond therapeutic concentrations and therefore cause DITD, which particularly could occur in polypharmacy patients.

Saliva could also play a role in the underlying mechanism of DITD. Saliva protects the external environment of the taste receptor cells and acts as a solvent and transportation medium for taste substances (Matsuo, 2000). Many drugs are known to cause quantitative or qualitative changes in saliva (Wolff et al., 2017). Almost 45% of the drugs known to potentially cause DITD coincided with dry mouth as an adverse effect, suggesting that there is at least some correlation. However, the exact correlation is difficult to assess since both MedDRA and the data that underlie the IM do not clearly discriminate between subjective “xerostomia” and objective “hyposalivation.” The term “dry mouth” is presumably used for both.

A healthcare professional confronted with a patient with DITD should assess which drug, or drug combination, is presumably responsible for the DITD. This can be done by comparing the temporal onset of DITD with the alterations in the drug usage (e.g., dosage, new drugs). However, as stated before, it is possible that DITD occurs months or years after the initial usage, complicating



the assessment of a temporal relationship. Another possibility is to consult pharmaceutical databases and overviews like the approach used in the present study.

Cessation of the drug responsible for DITD will most likely result in a decrease and eventually even recovery of DITD, but this (partial) recovery could take months. If cessation and alterations are not possible, other treatment modalities could be considered to relieve the symptoms. The evidence behind these modalities is scarce and based on research on taste disorders with other causes than DITD. Proposed treatment modalities include improving oral hygiene, suppletion of zinc, stimulation food flavors, saliva substitutes, and administration of alpha lipoic acid (Briggs, 2009; Femiano, Scully, & Gombos, 2002; Kumbargere Nagraj et al., 2017; Schiffman, 2018).

5 | CONCLUSION

Healthcare professionals are frequently confronted with drugs that are documented with DITD. The exact incidences of DITD remain unclear. This overview supports clinicians in their awareness, diagnosis, and possible treatment of DITD, and could serve as a reference for future research reporting on DITD.

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CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTION

All authors contributed to some extent to the current paper. WR was responsible for the study design, data collection, data analysis and drafting of the paper. YA, AH, KC all supported the data analysis and drafting the current paper. JL, AV supported the drafting of the current paper. FR guided the process from study design to drafting the current paper.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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